ELSEVIER
Journal of Cystic Fibrosis 11 (2012) 246 – 252
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Voriconazole pharmacokinetics and photosensitivity in children with cystic fibrosis

Sophia L. Markantonis [a,*], Anna Katelari [b], Eleni Pappa [a], Stavros Doudounakis [b]

[a] *Athens University, Faculty of Pharmacy, Laboratory of Biopharmaceutics and Pharmacokinetics, 157.71, Athens, Greece*
[b] *Cystic Fibrosis Unit, "Aghia Sophia" Children's Hospital, Athens, 11762,Greece*

Received 7 June 2011; received in revised form 21 December 2011; accepted 29 December 2011
Available online 28 January 2012

Abstract

Background: A high incidence of adverse skin reactions following long-term oral administration of voriconazole in children with cystic fibrosis and allergic bronchopulmonary aspergillosis (ABPA). The aim was to study the pharmacokinetics of voriconazole in these patients and to determine a possible association between drug levels and adverse effects.
Methods: Multiple venous blood samples were collected for HPLC determination of voriconazole concentrations and routine blood tests. Adverse events were recorded.
Results: No significant correlation was found between incidence of photosensitivity and voriconazole serum levels in 6 of 8 children with ABPA. 80% of patients had trough voriconazole concentrations<1000 ng/mL and were highly variable.
Conclusions: Long-term voriconazole therapy and greater sun exposure in Greece appear to play a major role in the occurrence of photosensitivity. Steady-state plasma drug concentrations were found to be highly variable and below the recommended therapeutic range in most patients, without any apparent negative influence on outcome.

Keywords: Voriconazole; Pharmacokinetics; Photosensitivity; Cystic fibrosis; Allergic bronchopulmonary aspergillosis

1. Introduction

Aspergillus spp and *Scedosporium* apiospermun are the most common filamentous fungi associated with clinical manifestations in patients with cystic fibrosis. Of these, *Aspergillus fumigatus* is by far the most isolated from respiratory specimens and can cause a wide range of diseases including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma in pre-existing pulmonary cavities and invasive pulmonary aspergillosis in immunocompromised patients. The most frequent manifestation of *Aspergillus* spp is ABPA with a prevalence of approximately 1–15% in patients with cystic fibrosis [1].

The triazole antifungal drug, voriconazole (VRZ), has almost completely replaced amphotericin B for the treatment of aspergillosis [2]. For the management of ABPA, oral glucocorticoids remain primary therapy, but VRZ is now considered to be a significant adjunct to therapy, in particular in patients with serious complications from or refractory to corticosteroids. Only 2 prospective clinical trials have documented VRZ pharmocokinetics in children [3,4] and only 3 retrospective reviews have dealt with therapeutic/toxic outcomes of VRZ therapy in children specifically undergoing treatment for ABPA [5–7]. In the study of Hilliard et al. [5], 13 pediatric CF patients with ABPA participated, 3 experienced adverse effects (2 photosensitivity skin reactions and one hair loss), 3 a drop in IgE levels post treatment and steroid dosing was not decreased. In contrast, Glackin et al. [6] reported that only one out of 9 patients developed minor side effects (visual disturbance and photosensitivity), but a mean decrease in IgE levels post treatment as well as a decrease in steroid dosing. Neely et al. [7] reported liver function test abnormalities not

* Corresponding author at: Faculty of Pharmacy, Department of Pharmaceutical Technology, Laboratory of Biopharmaceutics and Pharmacokinetics, University of Athens, Panepistimiopolis, Athens 157.71, Greece. Tel.: +30 210 7274676; fax: +30 210 7274027.
E-mail address: kyroudi@pharm.uoa.gr (S.L. Markantonis).

1569-1993/$ -see front matter © 2012 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.jcf.2011.12.006

significantly associated with VRZ concentrations and a pharmacodynamic association between VRZ trough concentrations >1000 ng/ml and survival.

Visual disturbances (photophobia or blurred vision), liver function test abnormalities and skin rashes/photosensitivity are the most common adverse events ascribed to VRZ, and relationships between VRZ mean or random concentrations and these side effects have been found [8,9], with the exception of adverse effects on the skin. Recently, several reports have associated long-term voriconazole therapy with skin reactions such as photosensitivity [10], the development of skin cancer [11,12] and severe phototoxicity [13]. The incidence of photosensitivity / rashes has been reported to be 14% [5],16%[3] and 17.3%[14]. In the Cystic Fibrosis centre of the Children's Hospital, "Aghia Sophia", Athens, the incidence of photosensitivity in 8 ABPA patients treated with VRZ for a period of >6 months was particularly high (75%) and prompted this study of the pharmacokinetics of VRZ in cystic fibrosis patients, primarily to determine if VRZ levels or other factors contributed to the occurrence of this side effect in these patients.

1.1. Aim of the study

In view of the observed high incidence of adverse skin reactions following long-term oral administration of voriconazole in children with cystic fibrosis and ABPA, our aim was to study the pharmacokinetics of VRZ in patients with cystic fibrosis and fungal infections, in particular those with ABPA, and to determine if drug levels achieved could possibly be associated with the occurrence of these or other adverse effects.

2. Patients and methods

2.1. Study design

A prospective, open-labeled, uncontrolled observational study. The study protocol was approved by the Scientific and Ethics Committees of the "Aghia Sophia" Children's Hospital, Athens. Written informed consent was obtained from parents/carers of each child.

2.2. Patients and methods

In all, 10 CF patients, five male and five female, with median age 14.8 years (range: 10–19) entered the study. Diagnosis of CF in all patients was based on typical clinical presentation together with at least two positive sweat chloride tests and two CF causing CFTR mutations. 8 of the patients had evidence of ABPA according to current diagnostic criteria [15] that included 5 or more of the following : a) acute or sub acute clinical deterioration in lung function (FEV1) not attributable to another etiology, b) total serum IgE>500 IU/ml, c) immediate cutaneous reactivity to *Aspergillus*, d) presence of serum IgE antibodies to *A. fumigatus*, e) precipitans/IgG antibodies to *A. fumigatus* , f) new or recent pulmonary infiltrates, mucus plugging or bronchiectasis that had not cleared with antibiotics and standard physiotherapy. Of the remaining 2 patients one had *Aspergillus* Bronchitis and one Scedosporium apiospermum exacerbation.

Patients were originally prescribed VRZ only if they did not meet any of the following exclusion criteria: use of concomitant medications known to be inhibitors, inducers or in any way interact with voriconazole, a history of hypersensitivity to azoles, liver disease defined as serum transaminase values more than twice the upper normal limit or serum bilirubin>50 mmol/L.

Each patient received 100 or 200 mg voriconazole twice a day depending on body weight. One blood sample was collected from each patient for genetic analysis. For voriconazole concentration measurements, venous blood was sampled, at steady state, just before drug administration and at 1, 2 and 4 h thereafter. The samples for VRZ analysis were centrifuged immediately at 3500 rpm for 5 min at approximately 4 °C, and the acquired plasma was stored at −70 °C until analysis.

At each trial visit, patients were asked whether they had experienced or were experiencing any adverse events with non-leading questions.

At the screening visit and fortnightly thereafter, blood was sampled for liver function tests and routine blood chemistry. For most hematological and biochemical tests pathological limits were set as defined by Lippert & Lehmen [16]. For enzymes the lower pathological limit was set at zero and the upper limit at twice the upper limit of normal.

2.3. Patient data collected and recorded

For each patient, the age, sex, weight, height, serum creatinine values, hepatic and renal function tests (aspartate aminotransferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γGT) and serum creatinine (SrCr)), voriconazole dose and duration of administration, concomitant drug therapy were recorded.

2.4. Quantitative analysis of plasma samples

Voriconazole plasma concentrations were determined using a previously validated HPLC method [17]. The dynamic range of the assay was 200 to 10,000 ng/ml. The lower limit of quantification was 100 ng/ml. At 200 ng/ml the inter-day coefficient of variation (c.v.) was 7.46%, at 600 ng/ml, 4.3%, at 4000 ng/ml 1.85% and 10,000 ng/ml, 1.21%, while the intra-day c.v. at 200 ng/ml was 0.6%, at 600 ng/ml, 0.58%, at 4000 ng/ml, 0.53% and 10,000 ng/ml , 0.51%. A total of seven calibration standards were prepared per analytical run.

2.5. DNA extraction and genotyping

DNA was extracted from peripheral blood leukocytes using the Blood DNA kit (QiAgen, Germany) according to standard protocols. Polymorphisms of *CYP2C19*2* (rs4244285) and *CYP2C19*3* (rs4986893) were analysed using a real-time polymerase chain reaction (PCR) allelic discrimination assay with a Lightcycler LC 480 Instrument (Roche diagnostics, Germany).

2.6. Statistical analysis

Quantitative variables are expressed as mean ± standard deviation (SD) for normally distributed variables, or as median and range when distribution departed from normality. For each patient, the age, weight, height, sampling time, administered dose, hepatic and renal function test values, achieved concentrations of VRZ in serum and all pharmacokinetic parameters were defined as quantitative continuous variables. All reported P values are two-sided. Pearson correlation tests were performed and a P value of <0.05 was considered statistically significant. Statistical processing and data analysis were performed with GraphPad Prism 4 software (GraphPad Software Inc.).

2.7. Pharmacokinetic evaluations

Single dose and multiple dose paediatric studies have concluded that voriconazole pharmacokinetics could be described by a linear pharmacokinetic model [14]. Hence, pharmacokinetic parameters of VRZ in serum were estimated from concentration-time data of individual patients by non-compartmental, steady-state analysis using the WinNonLin pharmacokinetic software package (Pharsight Co. Mountain View, CA).

3. Results

Patient characteristics, details of VRZ and concomitant drug therapy are presented in Table 1. Adverse effects ascribed to VRZ are shown in Table 2. Examples of study patients presenting photosensitivity during VRZ treatment (Fig. 1). Laboratory values regarding liver and renal function tests during VRZ treatment were within normal ranges, with the exception of the γGT levels in 1 patient, AST, ALT and γGT levels in 2 patients (Table 2). ALP levels were above normal (median 232 (range: 137–555)) in all but 1 patient (patient 6). Steady-state pharmacokinetic parameters of VRZ are presented in Table 3 and individual concentration-time curves of VRZ in the children with cystic fibrosis, with and without ABPA are shown in Fig. 2.

Determination of the *CYP2C19* genotype of all study patients, except patient 3, yielded the following results : Patient 2 was found to be heterozygous for the genetic variant *CYP2C19*2* enzyme (G/A, rs4244285) and homozygous wild type for the *CYP2C19*3* (G/G, rs4986893) and thus a poorer (intermediate) metabolizer of *CYP2C19* substrates; patient 9 was characterized as a homozygous poor metabolizer at *CYP2C19*2* and homozygous wild type for the *CYP2C19*3*, while the remaining patients were found to be homozygous wild type for both *CYP2C19*2* and *CYP2C19*3* and thus would be expected to metabolize the drug more extensively.

Table 1
Patient characteristics, voriconazole and concomitant drugs administration.

Patient	Sex	Age (years)	Weight (kg)	Dose of voriconazole (mg)*1	Days of therapy prior to sampling	Oral steroids	Antimicrobial agents administered during voriconazole treatment	Other medications
1	F	15.4	54	200	112	N	Amoxicillin and clavulanic acid, gentamicin (inh)	Pancreatic enzymes, Vits A,D,E, acetylcysteine
2	F	16.7	54	200	395	Y	Colistin(inh)	Pancreatic enzymes, Vits A,D,E, salbutamol
3	F	16.8	41	200	411	N	Azithromycin, tobramycin(inh), colistin(inh)	Pancreatic enzymes, Vits A,D,E,K, alendronate, bromhexine
4	F	13.4	34	100	20	N		Pancreatic enzymes, Vits A,D,E,K, acetylcysteine
5	F	12.5	28	100	338	N	Minocycline, colistin(inh)	Pancreatic enzymes, Vits A,D,E,K, acetylcysteine, dornase Alpha
6	M	19	60	200	373	N	Azithromycin, gentamicin(inh)	Pancreatic enzymes, Vits A,D,E,K, montelukast
7	M	10.3	36	100	360	Y	Cotrimoxazole, colistin(inh)	Pancreatic enzymes, Vits A,D,E, acetylcysteine, salbutamol
8	M	15.2	41	200	322	N	Cotrimoxazole, gentamicin(inh)	Pancreatic enzymes, Vits A,D,E,K, ursodiol, acetylcysteine
9	M	14.8	40	200	448	Y	Tobramycin (inh)	Pancreatic enzymes, Vits A,D,E,K, alendronate, ursodiol, bromhexine, montelukast, salbutamol, dornase Alpha
10	M	11.6	58	200	210	Y	Amoxicillin and clavulanic acid, colistin (inh)	Pancreatic enzymes, Vits A,D,E,K, acetylcysteine, montelukast

*1 twice a day; shaded rows patients without Allergic bronchopulmonary Aspergillosis (ABPA); inh :inhaled.

Table 2
Observed adverse effects from voriconazole therapy.

Patient	Liver function tests	Skin reactions	Optical reactions	CNS	Others
1					
2					
3	Increase in GGT between days 72 and 123	Photosensitivity, hair loss			
4					
5		Mild photosensitivity			
6					
7	Increase in AST, ALT, GGT-treated	Photosensitivity			
8		Photosensitivity, dermatitis	Optical disturbances	Headaches	
9	High AST, ALT, GGT	Photosensitivity, cheilitis	photophobia		Tremor
10		Photosensitivity			

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transpeptidase.

4. Discussion

4.1. Adverse effects

Six of the 8 children with ABPA (75%) experienced adverse effects attributable to VRZ (Table 2). All six ABPA patients developed photosensitivity reactions, of these one patient also developed dermatitis, optical disturbances and headaches, one cheilitis and tremor and one exhibited hair loss. Photosensitivity reactions were particularly troublesome for our paediatric patients in particular in view of their consistent nature and the need for long-term VRZ administration. No significant correlation was found between the incidence of photosensitivity and VRZ serum levels.

Various mechanisms for VRZ –induced photosensitivity have been proposed. Based on the fact that CF patients commonly receive vitamin A supplementation, Denning and Griffiths [18] first hypothesized that VRZ may inhibit a step in the breakdown of all-trans-retinol resulting in the accumulation of its intermediate metabolite, all-trans retinoic acid or tretinoin, known to cause various skin reactions sensitive to exposure to ultraviolet light. Cheng et al. [19] also believed that this mechanism may have been responsible for the cutaneous manifestations they encountered in five of six CF patients receiving VRZ. Another theory produced by Denning and Griffiths [18] was the possibility that VRZ or one of the by-products of its metabolism could elicit a phototoxic reaction. Subsequently, Cowen et al. [12], in a retrospective review published in 2010 suggested that VRZ photosensitivity may not be a result of the drug itself but its major metabolite, voriconazole N-oxide, which has been found to absorb in the UVA and UVB ranges and thus may act as a chromophore for phototoxicity.

Our study patients were all receiving vitamin A supplements, but in view of the fact that: only six of the ten study patients developed photosensitivity; VRZ inhibition of hepatic cytochrome p-450 enzymes has not been confirmed in vivo; routinely measured retinol levels were within normal limits; the retinol plasma levels required to produce various skin rashes is unknown and that a relationship between VRZ metabolism and phototoxicity has not yet been confirmed, we cannot attribute the frequent occurrence of photosensitivity in our patients to accumulation of either retinoic acid or voriconazole N-oxide.

Photosensitivity skin reactions are however clearly associated with long-term VRZ therapy[10,14,18]. Our ABPA patients all received VRZ for over 6 months. We believe that it is possible that the higher incidence of photosensitivity in our patients was mainly due to greater exposure to sunlight bearing in mind

Fig. 1. Photosensitivity/rash during voriconazole treatment.

Table 3
Steady-state pharmacokinetic parameters of voriconazole, estimated from the concentration-time data by non-compartmental analysis, following its oral administration to pediatric patients with cystic fibrosis (N=10).

No.	Dose (mg/12h) h)	Cmin ng/mL)	Cmax (ng/mL)	Cssave (ng/mL)	t½ (h)	$AUC_{0\text{-}12h}$ (mg*h/L)
1	200	611	3204	610.5	4.4	17.6
2	200	690	3030	690.3	4.8	18.4
3	200	2313	3918	2312.5	15.0	36.7
4	100	207	633	207.2	7.3	5.1
5	100	244	708	243.6	7.2	5.0
6	200	382	1429	382.1	6.2	8.4
7	100	218	654	217.9	9.7	4.2
8	200	584	2523	584.3	4.8	17.5
9	200	1547	5673	3395.1	5.5	42.4
10	200	468	1852	468.4	5.7	10.9

Shaded rows: patients without ABPS; Cmax: maximum voriconazole plasma concentration; Cmin: drug concentration at 0 hours i.e. the 12 hour-sample of the previous dose; Cave=steady-state average concentration; $AUC_{0-12\ h}$: area under the curve from the time of dosing to the time of next dose curve, determined by trapezoidal rule from the first to the last data point ($AUC_{all}=AUC_{0-12}$); $t_{1/2}$: elimination half-life was calculated as $\ln 2/\lambda_Z$, where λ_Z was estimated by log linear regression of the terminal portion of the plasma concentration-time curve (based on the last three data points);

the extent of sun exposure throughout the year in Athens, Greece. All patients were warned to avoid sunlight during treatment, but considering the basic need for all children to participate in outdoor activities (particularly male patients), it may arguably have been difficult for them to adhere to these precautions.

Three patients had clinically significant elevations in hepatic enzymes: AST, ALT and γ-GT levels (patients 7 and 9) and γ-GT levels (patient3). Peak serum VRZ levels in patients 9 and 3 were the highest noted among those study patients who were prescribed a 200 mg×2 daily VRZ dose (Table 3), while in patient 7, VRZ levels were low following a 100 mg×2 dose (Table 3). After decreasing the dose of VRZ, patient 9 presented an improvement in hepatic function and when the full dose of VRZ was restarted the side effect did not reappear. The risk of AST, ALP but not ALT abnormalities was found to be statistically associated to VRZ plasma concentrations in one study [8] and to increase by 7%–17% for every 1 μg/ml increase in concentration in another [9]. This association was apparent in patients 3 and 9, but not in patient 7. Among the liver function tests, only γ-GT levels were found to statistically associated with Cmax and Cmin VRZ serum levels (p=0.0374 and <0.0001) in our study.

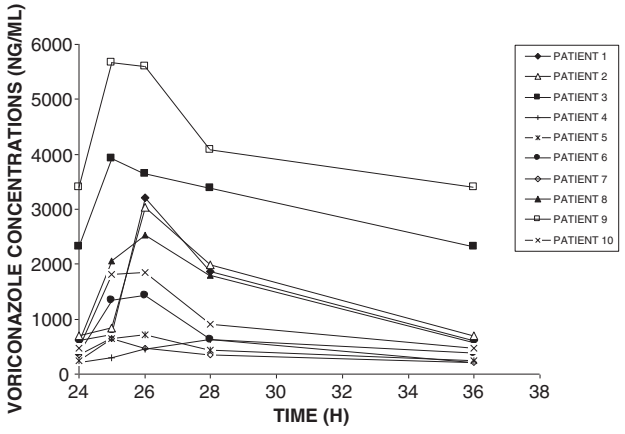

Fig. 2. Voriconazole steady-state concentrations in 10 pediatric study patients with cystic fibrosis.

Visual disturbances were noted in only two patients (patients 8 and 9) despite the fact that these have been reported to be the most common adverse effects of VRZ [3,8,20,21]. A significant relationship between plasma VRZ concentration and the odds of a visual adverse event has been revealed. The probability of a visual adverse event has been found to increase from 18 to 31%, with a change in plasma concentration from 0 to 9 mg/L [8]. The Cpssave of VRZ in patient 9 was the highest among the 10 study patients (3395.1 ng/L) and this supports the existence of the above relationship, but in patient 8 the Cpssave was not exceptionally high (584.3 ng/L) (Table 3).

4.2. Voriconazole pharmacokinetics

VRZ maintenance doses, 100 and 200 mg twice daily (2.8 to 5.0 mg/kg), produced highly variable drug levels in plasma e.g. Cmax and AUC values from 200 mg doses ranged between 1429 and 5673 ng/mL and 8.4 and 42.4 mg h/L, respectively. (Fig. 2, Table 3). However, when VRZ doses were considered based on mg/kg, significant correlations were found between the doses received and achieved Cmax values (p=0.0037) and estimated AUC values (p=0.0015). Cpave values were also found to be significantly correlated with the mg/kg dose (p=0.0083). Consequently, the different mg/kg doses administered to the study patients contributed to the observed variability in VRZ concentrations. Other factors that have been found

to be associated with this large variability include, in pediatric patients, age and genetic polymorphism of the cytochrome *CYP2C19* [3,22] and in cystic fibrosis, abnormal disposition of drugs leading to pharmacokinetic changes such as increased volume of distribution, decreased plasma concentration and enhanced renal and non-renal elimination [23].

With increasing age the near-linear pharmacokinetics of VRZ, described in children (2 to <12 years old) [3,14], becomes non-linear and as our patients were aged between 10 and 19 years, this could also have contributed to the variability observed. Furthermore, as allelic polymorphisms of *CYP2C19* have been reported to strongly influence voriconazole exposure [24], the *CYP2C19* genotype of all the patients, except for patient 3, were determined. Patient 2 was characterized as a poorer (intermediate) metabolizer and patient 9 as a homozygous poor metabolizer of *CYP2C19* substrates, while the remaining patients were characterized as more extensive metabolizers. In line with these findings, the highest $AUC_{0-12\,h}$ and Cmax values for VRZ were found for Patient 9, followed by patient 3 (for whom the genotype could not be determined), and then by patient 2, suggesting that VRZ exposure in the study patients may have been influenced by genotype as well.

Estimated t1/2 values, ranged from 4.4 to 9.7 h (mean 6.4 h) in 9 of the 10 patients, compared with a reported t1/2 of 6–9 h [25]. In one patient (patient 3) our t1/2 estimation was longer than the duration of sampling (see Table 3) and therefore must be regarded only as a rough estimation.

Trough VRZ concentrations, in the present study, ranged between 207 and 2313 ng/mL (Table 3). In the study of Pascual et al. [22] a trough VRZ concentration of 1 mg/L was found to be associated with a 70% probability of a successful outcome and in the study of Neely et al. [7] this trough level was found to be pharmacodynamically associated with survival. Eight of our study patients had trough VRZ concentrations < 1000 ng/mL and were highly variable, probably as a result of variability in absorption of VRZ [7] (Table 3). Delayed drug absorption in cystic fibrosis patients is considered to be due to altered GI physiology [23].

Higher mean VRZ concentrations tend to have better responses, with optimal outcomes observed with mean concentrations of 3000–4000 ng/mL [14]. Only in one patient (patient 9) were Cpave concentrations within this range. Despite what appear to be sub-therapeutic VRZ concentrations in the majority of our study patients, the use of VRZ in our patients with CF and ABPA led to serological improvement (total serum IgE, specific IgE on RAST), a lower frequency and adequate control of exacerbations and tapering of the steroid dose to the extent that 60% of our patients were not on steroid therapy at the time of this study [26] (Table 1). A possible partial explanation for the apparent efficacy of sub-therapeutic VRZ serum levels, may be the reported substantial penetration of VRZ into the pulmonary epithelial lining fluid achieving levels much higher than the minimum inhibitory concentrations of *Aspergillus* species (~0.5 mg/L) at the pulmonary site [27]. However, the clinical relevance of this finding has not been yet to be established.

We acknowledge that our study has some limitations. Our observations with respect to efficacy and sub-therapeutic VRZ serum levels suggest that recommended therapeutic trough levels should be lower in this patient group. However, our study was not powered to study this relationship and our data insufficient to support this finding. A suitably designed future study, which should include individual patient analysis of an adequate number of participants, is required to identify the subgroup of patients who might benefit from lower therapeutic VRZ levels. Furthermore, the possible role of the major metabolite, voriconazole N-oxide, in triggering photosensitivity [12] was not investigated in our study, as metabolite levels were not measured. The contribution of this metabolite to photosensitivity should be investigated in future. Finally, recent studies [24,28] have shown that the *CYP2C19*17* variant, associated with ultra rapid VRZ metabolism, may be partly responsible for variability in VRZ exposure and our study patients were not tested for this variant. Further investigation is needed to verify the involvement of the *CYP2C19*17* variant in the observed variation in VRZ pharmacokinetics.

5. Conclusions

Our preliminary data, from a small group of cystic fibrosis patients with ABPA, suggest that VRZ concentrations are not associated with observed photosensitivity in these patients. Long-term VRZ therapy appears to play a major role in the occurrence of photosensitivity, as may, we believe, greater sun exposure during spring, summer, autumn and even winter in Athens, Greece.

VRZ pharmacokinetics in children are highly variable, and this was confirmed in our cystic fibrosis patients with ABPA. The difference in mg/kg doses and *CYP2C19* genotype appear to contribute to this variability. The long-term administration (>6 months) of 100 or 200 mg twice daily VRZ doses achieve steady-state concentrations below the range for optimal outcome in some ABPA patients, without any apparent negative influence on outcome. Further suitably powered studies, to assess the relationship between VRZ pharmacokinetics and outcomes in cystic fibrosis patients with ABPA are warranted.

Ethical approval

Obtained from the Scientific and Ethics Committees of the "Aghia Sophia" Children's Hospital, Athens.

References

[1] Müller FM, Seidler M. Characteristics of pathogenic fungi and antifungal therapy in cystic fibrosis. Expert Rev Anti Infect Ther 2010;8(8):957–64.
[2] Prasad PA, Coffin SE, Leckerman KH, Walsh TJ, Zaoutis TE. Pediatric antifungal utilization: new drugs, new trends. Pediatr Infect Dis J 2008;27:1083–8.
[3] Walsh TJ, Karlsson MO, Driscoll T, Arguedas AG, Adamson P, Saez-LLorens X, et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob Agents Chemother 2004;48:2166–72.
[4] Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. Antimicrob Agents Chemother 2009;53(3):935–44.

[5] Hilliard T, Edwards S, Buchdahl R, Francis J, Rosenthal M, Balfour-Lynn I, et al. Voriconazole therapy in children with cystic fibrosis. J Cyst Fibros 2005;4:215–20.
[6] Glackin L, Leen G, Elnazir B, Greally P. Voriconazole in the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis. Ir Med J 2009;102(1):29.
[7] Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis 2010;50:27–36.
[8] Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. J Clin Pharmacol 2006;46(2):235–43.
[9] Lutsar I, Hodges MR, Tomaszeewski K, Troke PF, Wood ND. Safety of voriconazole and dose individualization. Clin Infect Dis 2003;36:1087–8.
[10] Malani AN, Aronoff DM. Voriconazole-induced photosensitivity. Clin Med Res 2008;6(2):83–5.
[11] McCarthy KL, Playford EG, Looke DF, Whitby MQ. Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. Clin Infect Dis 2007;44(5):e55–6.
[12] Cowen EW, Nguyen JC, Miller DD, McShane D, Arron ST, Prose NS, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatol 2010;62(1):31–7.
[13] Vöhringer S, Schrum J, Ott H, Höger PH. Severe phototoxicity associated with long-term voriconazole treatment. J Dtsch Dermatol Ges 2011;9(4): 274–6.
[14] FDA Antiviral Drugs Advisory Committee. Briefing Document for Voriconazole (Oral and Intravenous formulations), 2001. [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_01_Pfizer.pdf]
[15] Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, et al. Participants in the Cystic Fibrosis Foundation Concensus Conference. Clin Infect Dis 2003;37(Suppl. 3):S225–64.
[16] Lippert H, Lehmann HP. SI units in Medicine: an introduction to the international system of units with conversion tables and normal ranges. First ed. Baltimore-Munich, USA: Urban & Schwarzenberg; 1978.
[17] Gage R, Stopher DA. A rapid HPLC assay for voriconazole in human plasma. J Pharm Biomed Anal 1998;17:1449–53.
[18] Denning DW, Griffiths CE. Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. Clin Exp Dermatol 2001;26:648–53.
[19] Cheng MP, Paquette K, Lands LC, Ovetchkine P, Theoret Y, Quach C. Voriconazole inhibition of vitamin A metabolism: are adverse events increased in cystic fibrosis patients? Pediatr Pulmonal 2010;45:661–6.
[20] Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis 2003;36:630–7.
[21] Racette AJ, Roenigk Jr HH, Hansen R, Mendelson D, Park A. Photoaging and phototoxicity from long-term voriconazole treatment in a 15-year-old girl. J Am Acad Dermatol 2005;52(5 Suppl 1):S81–5.
[22] Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 2008;46(2):201–11.
[23] Prandote J. Clinical pharmacology of antibiotics and other drugs in cystic fibrosis. Drugs 1988;35(5):542–78.
[24] Berge M, Guillemain R, Tregouet DA, Amrein C, Boussaud V, Chevalier P, et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur J Clin Pharmacol 2011;67(3): 253–60.
[25] Azanza JR, Garcia-Quetglas E, Sadaba B. Pharmacology of azoles. Rev Ineroam Micol 2007;24:223–7.
[26] Katelari A, Lympari J, Kapi A, Xenofonte K, Doudounakis S. Voriconazole therapy in children with cystic fibrosis and steroid-dependent allergic bronchopulmonary aspergillosis: efficacy and adverse effects. 32nd European Cystic Fibrosis Conference; 2009.
[27] Capitano B, Potoski BA, Husain S, Zhang S, Paterson DL, Studer SM, et al. Intrapulmonary penetration of voriconazole in patients receiving an oral prophylactic regimen. Antimicrob Agents Chemother 2006;50(5):1878–80.
[28] Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol 2009;65:281–5.